oxocrinamine as short-bladed prisms, m.p. 165–167°, $[\alpha]^{24}_{589}$ + 203°, $[\alpha]^{24}_{436}$ +640° (*c* 0.56, ethanol). This compound depressed the melting point of oxohaemanthamine (m.p. 164–165°) nearly 20°. Oxocrinamine showed a band at 1748 cm.$^{-1}$ ($CHCl_3$) in the infrared and had an ultraviolet spectrum identical with that of oxohaemanthamine.

Catalytic Hydrogenation–Hydrogenolysis of Diacetylhaemanthidine.—A solution of 424 mg. of diacetylhaemanthidine[2,31] in 60 ml. of absolute ethanol was added to a suspension of 100 mg. of platinum oxide and 200 mg. of palladium-on-charcoal which had been equilibrated with hydrogen. The solution absorbed 1 mole of hydrogen at 28° in 30 minutes and absorption ceased. The temperature was raised to reflux the ethanol, and the solution absorbed another 23 ml. of hydrogen over a 2-hour period. The mixture was cooled and filtered. The solvent was removed under reduced pressure to yield 400 mg. of an oil. The residue was warmed with 10% sodium hydroxide for 4 hours, extracted with chloroform and dried over sodium sulfate. The chloroform was removed under reduced pressure to yield 350 mg. of a viscous oil which was dissolved in chloroform and chromatographed over alumina. Elution with 1% ethanol in chloroform produced 13 mg. (3.5%) of crystals which were sublimed at 150° (10 μ) to afford dihydrohaemanthamine, m.p. 228–230°, $[\alpha]^{25}_{589}$ +78 ± 2° (*c* 0.25, chloroform). The melting point of a mixture with authentic dihydrohaemanthamine prepared from haemanthamine was not depressed. The infrared absorption spectra (KBr) of the two materials were identical.

Further elution with 10% ethanol in chloroform yielded 250 mg. of dihydrohaemanthidine, identical in all respects with authentic material.

Many conditions were employed without success in an effort to improve the yield of dihydrohaemanthamine. In one case a 5% yield of dihydrohaemanthamine was obtained by conducting the reduction in hot glacial acetic acid with a small amount of perchloric acid in the presence of palladium-on-charcoal alone. The yield of dihydrohaemanthamine was so low in all of these reactions that it was felt necessary to ascertain that the haemanthidine used in the reactions contained no haemanthamine. To this end a 300-mg. mixture of 5% haemanthamine in haemanthidine was chromatographed over alumina and easily separated into its components with chloroform and 10% ethanol–chloroform, respectively. Haemanthidine purified in this manner was used in subsequent hydrogenations without affecting the results.

BETHESDA 14, MD.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

The Synthesis of 9-(2-Amino-2-deoxy-β-D-allopyranosyl)-6-dimethylaminopurine, an Analog of the Aminonucleoside Derived from Puromycin

BY FRANCIS J. MCEVOY, MARTIN J. WEISS AND B. R. BAKER[1]

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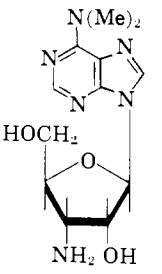
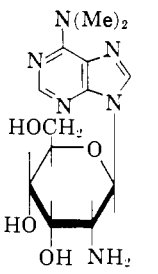
The subject nucleoside was prepared by a fifteen-step synthesis from N-anisylidene-D-glucosamine.

Analogs of the aminonucleoside[2] I derived from the antibiotic puromycin are of interest because of the antitumor[3] and trypanocidal[4] properties exhibited by I in experimental animals. Previous reports from this Laboratory have described the preparation of various analogs of I containing variations in the aminosugar moiety. These have included the 9-β 3-aminoarabinofuranosyl,[5] 3-aminoxylofuranosyl,[6] 5-aminoribofuranosyl[7] and 2-aminoribofuranosyl[8] derivatives of 6-dimethylaminopurine. In this paper we wish to report the synthesis of another such analog, 9-(2-amino-2-deoxy-β-D-allopyranosyl)-6-dimethylaminopurine (II).[9]

In principle, it was anticipated that the synthesis of a 2-aminoalloside could be achieved conveniently from a 2-aminoglucosyl nucleoside by inversion of the hydroxy group at C-3. Nucleosides containing the 2-aminoglucosyl sugar have been reported,[10]



I



II

and inversion of an hydroxy group adjacent and *trans* to an amino group *via* the N-acetyl-*O*-mesylate has been described in the carbohydrate field for both glycosides[11,12] and nucleosides.[13]

Previous reports from this Laboratory have described the synthesis in 47% yield of 9-(2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-β-D-glucopyranosyl)-6-dimethylamino-2-methylmercaptopurine (VI) from chloroacetoglucosamine (III) and chloromercuri-6-dimethylamino-2-methylmercaptopurine (V).[10,14] However, in the present investigation,

(1) Stanford Research Institute, Menlo Park, Calif.

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(8) F. J. McEvoy, B. R. Baker and M. J. Weiss, THIS JOURNAL, **82**, 209 (1960).

(9) The synthesis of 9-(3-amino-2-deoxy-β-D-allopyranosyl)-6-dimethylaminopurine will be reported at a later date (R. E. Schaub and M. J. Weiss).

(10) B. R. Baker, J. P. Joseph, R. E. Schaub and J. H. Williams, *J. Org. Chem.*, **19**, 1786 (1954).

(11) B. R. Baker and R. E. Schaub, *ibid.*, **19**, 646 (1954).

(12) B. R. Baker, R. E. Schaub and J. H. Williams, THIS JOURNAL, **77**, 7 (1955).

(13) B. R. Baker and R. E. Schaub, *ibid.*, **77**, 2396 (1955).

(14) The chloromercuri derivative of 6-dimethylamino-2-methylmercaptopurine was used rather than that of 6-dimethylaminopurine since it has been shown that reaction of the chloromercuri derivative of the latter purine with chloroacetoglucose gives a 7-substituted nucleoside, whereas condensation with the derivative of the former purine gives a 9-substituted nucleoside.[15] It was assumed that a similar course of reaction would obtain with a 1-chloro-2-acetamido-

we have been unable to effect this condensation in satisfactory yield. The poor yields may have been due to the presence of alkaline impurities in the chloromercuripurine (V) batches which were used. In any event, since *O*-benzoyl blocked halogenoses have been more satisfactory, at least in certain instances, for nucleoside condensations than the corresponding *O*-acetyl blocked halogenoses,[16,17] it seemed worthwhile to attempt this condensation with an *O*-benzoyl blocked glucosamine derivative.

The required halogenose, N-acetyl-3,4,6-tri-*O*-benzoyl-1-chloro-α-D-glucosamine (IV), was synthesized from N-anisylidene-D-glucosamine by the procedure reported for the preparation of the corresponding tri-*O*-acetate.[10,18] Thus, the N-anisylidene derivative was converted in 81% yield to 1,-3,4,6-tetra-*O*-benzoyl-D-glucosamine, which on acid hydrolysis followed by N-acetylation gave N-acetyl-1,3,4,6-tetra-*O*-benzoyl-D-glucosamine in excellent yield. From this latter compound, the desired halogenose IV was then obtained as a crystalline product in 45% yield by a titanium tetrachloride treatment, and in 74% yield by reaction with ethereal hydrogen chloride.[10] The α-configuration for the halogenose is assumed on theoretical grounds (the most stable conformational structure[19]) and by analogy.[10] Condensation of halogenose IV with chloromercuri-6-dimethylamino-2-methylmercaptopurine (V) in refluxing xylene afforded the blocked nucleoside VII as a dark gum which resisted crystallization. However, removal of the benzoyl blocking groups by methoxide-catalyzed methanolysis gave crystalline VIII[10] in 52% over-all yield for the two steps.

In order to set the stage for the inversion at C-3 it was necessary to preferentially block the hydroxyls at C-4 and C-6 prior to mesylation of the C-3 hydroxyl. This was conveniently achieved *via* the 4,6-*O*-benzylidene derivative IX which was prepared in 66% yield on treatment of VIII with benzaldehyde and fused zinc chloride. The free C-3 hydroxyl was then mesylated in 60% yield. Treatment of the resulting mesylate X with sodium acetate in refluxing 95% aqueous 2-methoxyethanol resulted in inversion of configuration at C-3 to give the 2-acetamidoalloside XI in 82% yield. This inversion presumably takes place by way of an oxazoline intermediate which is formed on displacement of the 3-mesyloxy group by the neighboring 2-acetamido group.[11] That an alloside actually is obtained is assumed on the basis of analogy[11-13] and from the fact that the tri-*O*-acetate XIV (see below) derived from this product is different from the corresponding derivative (VI) of 2-acetamidoglucose.

With the development of the 2-aminoalloside structure, all that was required for completion of the synthesis of II was the removal of the various blocking groups. As will be seen below, the N-acetyl and the *O*-blocking groups were hydrolyzed without difficulty. However, removal of the 2-methylmercapto group by a Raney nickel desulfurization treatment was troublesome. On the basis of preliminary experiments, it was thought that a major difficulty resulted from the essentially irreversible adsorption of the nucleoside on the Raney nickel. Since it was possible that this adsorption took place by an interaction of the free hydroxy groups with the nickel, it was reasonable to anticipate that this effect might be minimized with an *O*-acyl blocked derivative. Therefore, the tri-*O*-acetate XIV was prepared from XI by 3-*O*-acetylation to produce XII in 77% yield, followed by cleavage of the benzylidene group with dilute acid to give XIII as a non-crystallizable gum and finally 4,6-di-*O*-acetylation (57% for the last two steps).

Raney nickel treatment of tri-*O*-acetate XIV by the usual procedure[10] gave a 32% yield of the desulfurized product XV. Since any alkali present in the Raney nickel preparation could cause hydrolysis of the acetate blocking groups, the desulfurization was tried in the presence of a carboxylic acid resin (Amberlite IRC-50 ion exchange resin) resulting in a 53% yield of XV. As finally worked out, this transformation was carried out with Raney nickel, which had been partially deactivated by heating with refluxing acetone for two hours,[20] and in the presence of the Amberlite IRC-50 resin. In this way XV was obtained as a crude glass in 85% yield. Methoxide-catalyzed de-*O*-acetylation then smoothly afforded the N-acetyl blocked nucleoside XVI in 77% yield. Finally, barium hydroxide hydrolysis produced the desired analog II in 36% yield.

When tested against a transplanted mammary adenocarcinoma of the C_3H mouse, II was inactive and toxic at a dose of 5 mg. per mouse.

Acknowledgments.—We wish to thank Dr. H. M. Kissman for helpful discussions and technical assistance, Mr. J. Poletto of the Preparations Laboratory for the large-scale preparation of certain intermediates, Mr. L. Brancone and staff for microanalyses, Mr. W. Fulmor and staff for spectral and polarimetric determinations, and Dr. A. W. Vogel and staff of the Experimental Therapeutics Section of these laboratories for the tumor assays.

Experimental[21]

N-Anisylidene-3,4,6-tetra-*O*-benzoyl-D-glucosamine.—To a partial solution of 75 g. of N-anisylidene-D-glucosamine in 750 cc. of pyridine was added 150 cc. of benzoyl chloride portionwise and with swirling. The resulting solution was heated on the steam-bath for 2 hours, then poured into 2400 cc. of ice-water. A gum separated and the water was decanted. Upon trituration with 1000 cc. of water, the gum crystallized. The crystals were collected and washed twice with 500-cc. portions of water; yield 155.8 g. (81%) of white crystals, m.p. 168–170° dec.

A similar preparation, recrystallized several times from toluene, gave white crystals, m.p. 190–191°, $[\alpha]^{24}D$ +59.3° (1% in chloroform).

Anal. Calcd. for $C_{42}H_{35}NO_{10}$: C, 70.6; H, 4.91; N, 1.96. Found: C, 70.4; H, 5.18; N, 2.04.

glucose derivative. However, it may be noted that chloromercuri-6-dimethylaminopurine does react with certain sugars to give 9-substituted purines.[7,18]

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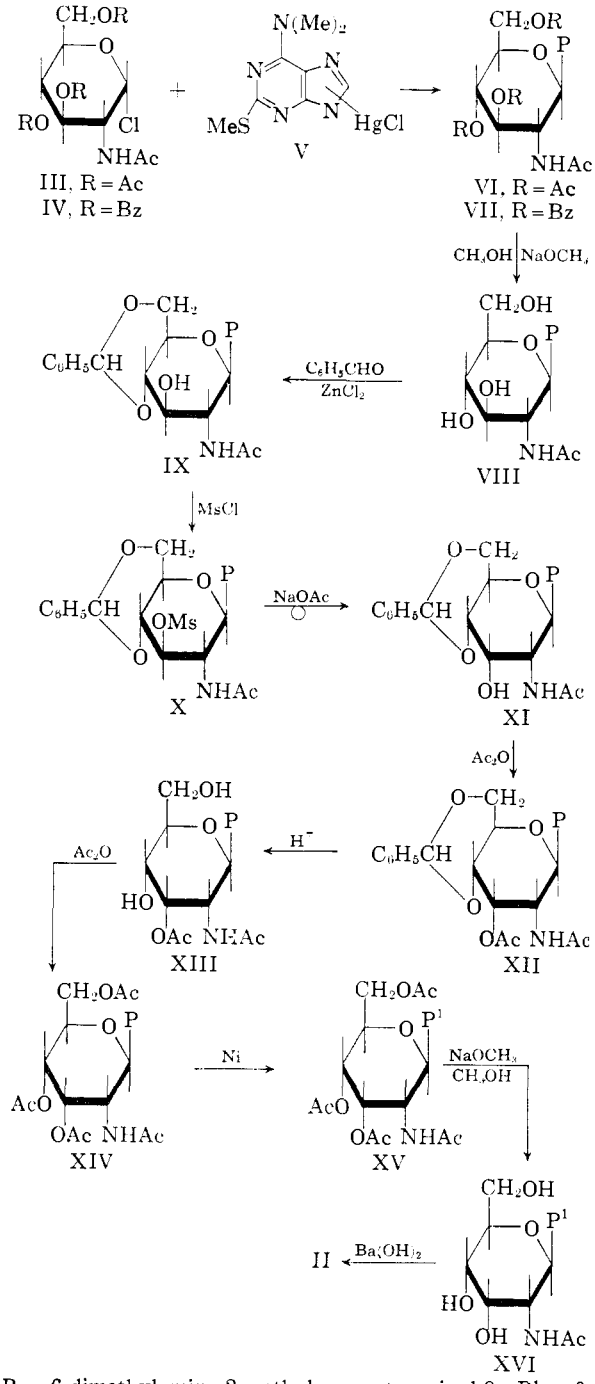
(21) Melting points are uncorrected.



P = 6-dimethylamino-2-methylmercaptopurinyl-9; P^1 = 6-dimethylaminopurinyl-9

1,3,4,6-Tetra-*O*-benzoyl-D-glucosamine · HCl.—To a hot solution of 1.0 g. of N-anisylidene-D-glucosamine tetrabenzoate in 5 cc. of acetone was added 1.4 cc. of 5 *N* hydrochloric acid. The solution was allowed to come to room temperature while crystals were separating. To the mixture was added 5 cc. of absolute ether and the mixture was cooled in an ice-bath for 30 minutes. The crystals were collected and washed with two 5-cc. portions of 1:1 ether–acetone solution; yield 820 mg. (93%) of white crystals, m.p. 200–201° dec.

Anal. Calcd. for $C_{34}H_{29}NO_9 \cdot HCl$: C, 64.5; H, 4.75; N, 2.22. Found: C, 64.1; H, 4.76; N, 2.35.

N-Acetyl-1,3,4,6-tetra-*O*-benzoyl-D-glucosamine.—To a mixture of 500 mg. of tetrabenzoylglucosamine· HCl, 2.0 cc. of pyridine and 0.5 cc. of acetic anhydride was added 75 mg. of anhydrous sodium acetate with stirring. Solution was practically complete. The solution was allowed to stand for 20 minutes. After the addition of 20 cc. of water, the solution was stirred for 10 minutes and then extracted with two 15-cc. portions of chloroform. The combined extracts were washed successively with excess saturated sodium bicarbonate solution, water, and two 10-cc. portions of 1% hydrochloric acid. The organic solution was dried with magnesium sulfate and evaporated under reduced pressure. The 450 mg. (89%) of residual colorless glass was analyzed; $[\alpha]^{24}D$ −19.3° (2% in chloroform).

Anal. Calcd. for $C_{36}H_{31}NO_{10}$: C, 67.8; H, 4.94; N, 2.20. Found: C, 67.8; H, 5.17; N, 2.42.

N-Acetyl-3,4,6-tri-*O*-benzoyl-1-chloro-α-D-glucosamine (IV) was prepared by two methods.[10]

(A) To a solution of 11.0 g. of N-acetylglucosamine tetrabenzoate in 70 cc. of chloroform was added a solution of 1.98 cc. of titanium tetrachloride in 10 cc. of chloroform. A yellow precipitate was formed immediately but this went into solution during 3.5 hours refluxing. The solution was cooled in an ice-bath and washed with two 15-cc. portions of ice-water and two 15-cc. portions of ice-cold, saturated sodium bicarbonate solution. The chloroform solution was dried over magnesium sulfate and the solvent was removed under reduced pressure at a bath temperature not exceeding 50°. The 8.9 g. of residual amber gum was dissolved in 25 cc. of absolute ether and kept at 5° for 3 days. The resultant crystals were collected and washed with two 10-cc. portions of absolute ether; yield 4.3 g. (45%), m.p. 128–130°.

(B) A solution of 137 g. of N-acetylglucosamine tetrabenzoate, dissolved in 137 cc. of acetyl chloride, was cooled to 3° and added to a cold (3°) solution of 1370 cc. of saturated ethereal hydrogen chloride. The solution was protected with a calcium chloride drying tube and kept at 3° for 4 days. The crystals that formed were removed under anhydrous conditions and the filtrate was immediately returned to the cold-room (3°). The crystalline material was washed with two 50-cc. portions of absolute ether, and 23.6 g. (20%) of white crystals, m.p. 126–127° dec., were obtained. Additional crops were removed on the eleventh and nineteenth days to bring the total yield to 86.5 g. (73.5%). Satisfactory analyses could not be obtained.

9-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-6-dimethylamino-2-methylmercaptopurine (VIII).—A mixture of thoroughly washed Celite[22] diatomaceous earth mix weighing 52.2 g. and containing 32.6 g. of the chloromercuri salt (V) of 2-methylmercapto-6-dimethylaminopurine and 1500 cc. of reagent toluene was stirred and heated while 250 cc. of toluene was distilled off.[9] The mixture was stirred and azeotropically refluxed under a constant water separator for 2 hours. The mixture was cooled to approximately 60°, and 40.5 g. of N-acetyl-3,4,6-tri-*O*-benzoyl-1-chloro-α-D-glucosamine (IV) was added. The mixture was stirred and refluxed for 20 hours and then filtered hot. The filter-cake was washed with chloroform until the washings were clear. The filtrate was evaporated under reduced pressure and the residue was shaken with a mixture of 500 cc. of chloroform and 250 cc. of 30% aqueous potassium iodide solution. The chloroform layer was separated, dried over magnesium sulfate, and evaporated to dryness under reduced pressure leaving a dark gum weighing 60 g. This crude condensation product (VII) was dissolved in 500 cc. of absolute methanol and 40 cc. of 1 *N* sodium methoxide was added. The solution was then refluxed for 30 minutes during which time its alkalinity was checked and maintained. The solution was evaporated to dryness under reduced pressure and the residue dissolved in 50 cc. of methanol. After chilling for 3 days, the precipitated solids were filtered and washed with two 15-cc. portions of methanol; yield 15.7 g. (52%) of tan crystals, m.p. 234–236° dec. This product was identical by mixed melting point and infrared comparison with the material prepared[10] *via* the tri-*O*-acetate III.

9-(2-Acetamido-2-deoxy-4,6-*O*-benzylidene-β-D-glucopyranosyl)-6-dimethylamino-2-methylmercaptopurine (IX).—A mixture of 15.7 g. of 9-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-6-dimethylamino-2-methylmercaptopurine (VIII) and 28.4 g. of freshly fused zinc chloride in 142 cc. of benzaldehyde was shaken for 20 hours, solution being complete in about 5 minutes. The solution was poured into 2000 cc.

(22) Celite, a product of the Johns-Manville Corporation, is the trademark for diatomaceous earth.

of absolute ether with stirring. The precipitated white solid was collected under anhydrous conditions and washed with absolute ether. The partially dried solid was dissolved in 1000 cc. of 2-methoxyethanol and 96.5 cc. of 10% sodium hydroxide was added. After standing at room temperature for 10 minutes, the solution was neutralized (phenolphthalein) with carbon dioxide gas. The solution was filtered from some white solid which was washed with two 80-cc. portions of hot 2-methoxyethanol. The combined filtrate and washings were evaporated to a semi-solid under reduced pressure. The residue was partially dissolved in 100 cc. of 2-methoxyethanol and 500 cc. of water was added with stirring. The product was collected and washed with two 80-cc. portions of 1:5 2-methoxyethanol–water to give 12.6 g. (66%) of tan crystals, m.p. 254–255° dec.

A similar preparation was recrystallized from ethyl acetate–heptane to give white crystals, m.p. 264–265° dec., $[\alpha]^{24}D$ +20.9° (1% in chloroform).

Anal. Calcd. for $C_{23}H_{28}N_6O_5S$: C, 55.4; H, 5.6; N, 16.8. Found: C, 56.3; H, 5.13; N, 16.6.

9-(2-Acetamido-2-deoxy-4,6-*O*-benzylidene-3-*O*-mesyl-β-D-glucopyranosyl)-6-dimethylamino-2-methylmercaptopurine (X).—To a solution of 7.1 g. of 9-(2-acetamido-2-deoxy-4,6-*O*-benzylidene-β-D-glucopyranosyl)-6-dimethylamino-2-methylmercaptopurine (IX) in 71 cc. of pyridine was added dropwise 2.5 cc. of methanesulfonyl chloride. The solution was protected with a calcium chloride drying tube and heated at 50–52° for 20 hours. The solution was poured into 285 cc. of ice-water with stirring, and the aqueous solution was extracted with two 250-cc. portions of chloroform. The combined extracts, dried over magnesium sulfate, were evaporated to dryness under reduced pressure. Trituration with 100 cc. of absolute ethanol yielded 4.9 g. (60%) of gray powder, m.p. 201–202° dec.

A similar preparation, on recrystallization from absolute ethanol, gave white crystals, m.p. 201–202° dec.

Anal. Calcd. for $C_{24}H_{30}N_6O_7S_2$: C, 49.8; H, 5.19; N, 14.5; S, 11.1. Found: C, 49.6; H, 5.46; N, 14.5; S, 11.0.

9-(2-Acetamido-2-deoxy-4,6-*O*-benzylidene-β-D-allopyranosyl)-6-dimethylamino-2-methylmercaptopurine (XI).—A solution of 375 cc. of 95% aqueous 2-methoxyethanol containing 15.7 g. of anhydrous sodium acetate and 6.3 g. of 9-(2-acetamido-2-deoxy-4,6-*O*-benzylidene-3-*O*-mesyl-β-D-glucopyranosyl)-6-dimethylamino-2-methylmercaptopurine (X) was refluxed for 20 hours. The solution was evaporated to dryness under reduced pressure and the residue dissolved in a mixture of 140 cc. of water and 280 cc. of chloroform. The organic solution was separated and washed with 140 cc. of water. The chloroform solution was dried with magnesium sulfate and evaporated to dryness under reduced pressure leaving a gum mixed with crystals. The residue was heated on the steam-bath with 50 cc. of toluene, then chilled in an ice-bath for 30 minutes. The product was washed with two 10-cc. portions of toluene to give 4.4 g. (82%) of white crystals, m.p. 229–231° dec.

A similar preparation was recrystallized from methanol to give white crystals, m.p. 239–240° dec.

Anal. Calcd. for $C_{23}H_{28}N_6O_5S$: C, 55.2; H, 5.60; N, 16.8. Found: C, 54.6; H, 5.96; N, 17.1

9-(2-Acetamido-2-deoxy-3-*O*-acetyl-4,6-*O*-benzylidene-β-D-allopyranosyl)-6-dimethylamino-2-methylmercaptopurine (XII).—To a solution of 180 mg. of 9-(2-acetamido-2-deoxy-4,6-*O*-benzylidene-β-D-allopyranosyl)-6-dimethylamino-2-methylmercaptopurine (XI) in 1.8 cc. of pyridine was added 1.8 cc. of acetic anhydride. The solution was heated on the steam-bath for 90 minutes and then poured into 18 cc. of ice-water. The aqueous solution was extracted with two 10-cc. portions of chloroform, and the combined extracts, dried with magnesium sulfate, were evaporated to dryness under reduced pressure. The residue was twice evaporated under reduced pressure with 10-cc. portions of toluene. The residual glass was crystallized from ethyl acetate–petroleum ether yielding 150 mg. (77%) of white crystals, m.p. 197–207° dec. Several recrystallizations from the same solvent mixture raised the melting point to 204–205° dec.

Anal. Calcd. for $C_{25}H_{30}N_6O_6S$: C, 55.4; H, 5.54; N, 15.5. Found: C, 54.8; H, 5.80; N, 15.3.

9-(2-Acetamido-2-deoxy-3-*O*-acetyl-β-D-allopyranosyl)-6-dimethylamino-2-methylmercaptopurine (XIII).—A solution of 500 mg. of 9-(2-acetamido-2-deoxy-3-*O*-acetyl-4,6-*O*-benzylidene-β-D-allopyranosyl)-6-dimethylamino-2-methylmercaptopurine (XII) in 25 cc. of 95% methanol (containing 0.5% hydrochloric acid) was refluxed for 30 minutes. When the solution was evaporated to dryness *in vacuo*, there remained a tan glass, weighing 400 mg. (96%), which could not be crystallized.

9-(2-Acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-β-D-allopyranosyl)-6-dimethylamino-2-methylmercaptopurine (XIV).—To a solution containing 350 mg. of 9-(2-acetamido-2-deoxy-3-*O*-acetyl-β-D-allopyranosyl)-6-dimethylamino-2-methylmercaptopurine (XIII) in 3.5 cc. of pyridine was added, 3.5 cc. of acetic anhydride. The solution was heated on the steam-bath for 75 minutes, then cooled and stirred with 20 cc. of water for 15 minutes. The aqueous solution was extracted with two 15-cc. portions of chloroform. The combined extracts were dried with magnesium sulfate and evaporated to dryness under reduced pressure. The evaporation was repeated twice with 10-cc. portions of toluene, and the residual gum was crystallized from ethyl acetate to yield 100 mg. of white crystals, m.p. 197–198°.

Anal. Calcd. for $C_{22}H_{30}N_6O_8S$: C, 49.0; H, 5.57; N, 15.6. Found: C, 48.8; H, 5.84; N, 15.0.

9-(2-Acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-β-D-allopyranosyl)-6-dimethylaminopurine (XV).—Maximum yields in the desulfurization reaction were obtained using a deactivated Raney nickel catalyst and a carboxylic acid resin.

(A) **Deactivated Raney Nickel Catalyst.**[20]—A mixture of 35 teaspoonfuls of Raney nickel (W-2) and 600 cc. of acetone was refluxed and stirred for 2 hours. The mixture was centrifuged and the acetone decanted. The nickel was slurried 3 times with 300-cc. portions of absolute ethanol, centrifuging and decanting the supernatant liquid each time. The deactivated nickel was then stored under absolute ethanol.

(B) **Carboxylic Acid Resin.**—Amberlite IRC-50 ion exchange resin (H)[23] was washed successively with 2 *N* hydrochloric acid, water, and absolute ethanol. The resin was then air-dried for 18 hours.

(C) **Desulfurization.**—A mixture of 32 g. of dry resin and 32 teaspoonfuls of deactivated Raney nickel in 50 cc. of absolute ethanol was stirred at room temperature for 10 minutes. To this mixture was added a solution of 16.0 g. of 9-(2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-β-D-allopyranosyl)-6-dimethylamino-2-methylmercaptopurine (XIV) in 1600 cc. of absolute ethanol. The reaction mixture was stirred and refluxed and the progress of the desulfurization was followed by noting the ultraviolet absorption of samples removed from the reaction mixture. The ratio of the intensity of absorption at 275 mμ to the intensity at 250 mμ should approach a value of 5.4 as the methylmercapto group is removed. In practice, the ratio of the extinction coefficients reached a value of 3.8 and became constant after one hour refluxing. The solution was filtered hot and the filter-cake washed with 500 cc. of hot ethanol. The combined filtrate and washings were evaporated to dryness under reduced pressure leaving a white glass weighing 12.5 g. (85%) which could not be crystallized.

9-(2-Acetamido-2-deoxy-β-D-allopyranosyl)-6-dimethylaminopurine (XVI).—A solution of 12.5 g. of 9-(2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-β-D-allopyranosyl)-6-dimethylaminopurine (XV) in 250 cc. of hot methanol and 2.7 cc. of 1 *N* sodium methoxide was refluxed for 30 minutes. The solution was evaporated to dryness under reduced pressure. The residue was crystallized by dissolving in 137 cc. of hot methanol and adding 690 cc. of hot heptane. A first crop of 3.6 g. of white crystals, m.p. 262–263° dec., was obtained when the solution reached room temperature. The filtrate on standing at 3° for 3 days produced a second crop weighing 3.2 g., m.p. 263–264° dec. A small third crop raised the total yield to 7.1 g. (77%). A similar preparation was analyzed.

Anal. Calcd. for $C_{15}H_{22}N_6O_5 \cdot {}^1/_2H_2O$: C, 48.0; H, 6.17; N, 22.11. Found: C, 47.9; H, 5.90; N, 21.84.

9-(2-Amino-2-deoxy-β-D-allopyranosyl)-6-dimethylaminopurine (II).—A solution of 1.00 g. of 9-(2-acetamido-2-deoxy-β-D-allopyranosyl)-6-dimethylaminopurine (XVI) in 100 cc. of saturated aqueous barium hydroxide solution was heated on the steam-bath for 20 hours. The solution was cooled, saturated with carbon dioxide gas and filtered. The filtrate on evaporation to dryness under reduced pressure left an amber gum weighing 681 mg. The gum was dissolved in 1:1 methanol–water solution and placed on an Amberlite IRC-

(23) Amberlite IRC-50 is the trademark of Rohm and Haas Co.

50 [H form] resin column.[24] The column was washed with 1:1 methanol–water mixture until the washes showed minimal absorption in the 274 mμ region. The column was then eluted with a 2 *N* ammonium hydroxide in 1:1 methanol–water solution, and the product was obtained by evaporation of the ammoniacal eluates under reduced pressure to yield 360 mg. (41%) of a white glass. Trituration of this glass with 10 cc. of ethyl acetate produced a white, amorphous solid weighing 320 mg., $[\alpha]^{24}D$ −5° (0.58% in MeOH).

(24) B. R. Baker, R. E. Schaub and H. M. Kissman, THIS JOURNAL, **77**, 5911 (1955).

Anal. Calcd. for $C_{13}H_{20}N_6O_4 \cdot {}^1/_2H_2O$: C, 46.83; H, 6.35; N, 25.21; H_2O, 2.70. Found: C, 46.90; H, 6.64; N, 25.15; H_2O, 2.86.

Crystallization and recrystallization from methanol (activated charcoal) gave material melting at 260–261°, $[\alpha]^{25}D$ −16.8° (1.01% in H_2O).

Anal. Calcd. for $C_{13}H_{20}N_6O_4$: C, 48.14; H, 6.22; N, 25.91. Found: C, 48.19; H, 6.40; N, 25.78.

PEARL RIVER, N. Y.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

Studies on the Synthesis of 9-(2-Amino-2-deoxy-β-D-ribofuranosyl)-6-dimethylaminopurine, an Analog of the Aminonucleoside Derived from Puromycin

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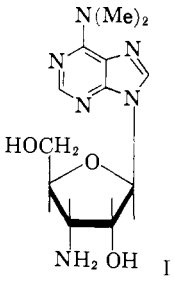
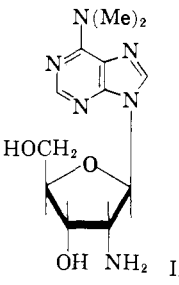
The synthesis of the subject nucleoside (II) was undertaken by a 14-step synthesis from methyl 3-amino-3-deoxy-4,6-*O*-benzylidene-α-D-altropyranoside (III) which is available in quantity from methyl α-D-glucopyranoside. Despite intensive efforts, II could not be obtained in crystalline form. However, the immediate precursor of II, compound XVIII, was crystalline and of unequivocal structure.

Analogs of the aminonucleoside I derived from the antibiotic puromycin[1] are of interest because of the antitumor[2] and trypanocidal[3] activities of I. Among the analogs of I, wherein the aminosugar moiety has been varied, and which have been prepared in our laboratory, are the 9-β,3-aminoarabinofuranosyl,[4] 3-aminoxylofuranosyl,[5] 5-aminoribofuranosyl,[6] 2-aminoallopyranosyl[7] and 3-aminoallopyranosyl[8] derivatives of 6-dimethylaminopurine. This paper describes our efforts to prepare 9-(2-amino-2-deoxy-β-D-ribofuranosyl)-6-dimethylaminopurine (II). Although these efforts were not attended with complete success, since the final product could only be obtained as a non-crystalline substance of somewhat doubtful purity, it seems worthwhile to record our results.



I



II

(1) For the chemistry of puromycin see B. R. Baker and co-workers, THIS JOURNAL, **77**, 12 (1955), and preceding papers.

(2) P. L. Bennett, S. L. Halliday, J. J. Oleson and J. H. Williams, "Antibiotics Annual 1954–1955," Medical Encyclopedia, Inc., New York, N. Y., 1954, pp. 766–769.

(3) R. I. Hewitt, A. R. Gumble, W. S. Wallace and J. H. Williams, *Antibiotics and Chemotherapy*, **4**, 1222 (1954).

(4) B. R. Baker and R. E. Schaub, THIS JOURNAL, **77**, 5900 (1955).

(5) R. E. Schaub, M. J. Weiss and B. R. Baker, *ibid.*, **80**, 4692 (1958).

(6) H. M. Kissman and B. R. Baker, Abstracts of Papers 130th Meeting of the A.C.S., Atlantic City, N. J., September, 1956, p. 19D; paper in preparation.

(7) F. J. McEvoy, M. J. Weiss and B. R. Baker, THIS JOURNAL, **82**, 205 (1960).

(8) R. E. Schaub and M. J. Weiss, to be reported.

In principle, the synthesis of II requires the preparation of a properly blocked 2-aminoribose derivative[9] in the furanoid configuration, its conversion to a 1-halo sugar and condensation of this halogenose with a suitable chloromercuripurine derivative. The previously reported[10] methyl 3-amino-3-deoxy-4,6-*O*-benzylidene-α-D-altropyranoside (III) was an attractive starting material since cleavage between C-1 and C-2 would directly afford the required 2-aminoribose structure. In addition, relatively substantial quantities of III can be prepared in four steps from the cheap and abundant methyl α-D-glucopyranoside, 2 kg. of which furnished 800 g. of III.

A convenient procedure for the degradation of a hexose to a pentose is the method of MacDonald and Fischer which proceeds *via* the hexose disulfone.[11] Our initial approach to this problem was an attempt to utilize this procedure. When the 3-aminoaltroside III was shaken with ethyl mercaptan and concentrated hydrochloric acid, there was obtained the diethyl mercaptal (IV) of 3-aminoaltrose · HCl. The crude product was acetylated with acetic anhydride in pyridine and the resultant pentacetate (V) was de-*O*-acetylated with methanolic sodium methoxide to give the crystalline diethyl mercaptal (VI) of 3-acetamidoaltrose in 35% over-all yield from III. Selective N-acylation of IV to give VI was not a satisfactory procedure.

In order to ensure the formation of the desired

(9) At the time of this investigation the only known 2-amino-2-deoxypentose was the D-xylose derivative synthesized by Wolfrom and Anno [THIS JOURNAL, **75**, 1038 (1953)] from glucosamine by cleavage of C-6 and reduction of the resulting 5-aldehyde. Since then Wolfrom, Shafizadeh and Armstrong [*ibid.*, **80**, 4885 (1958)] have reported the synthesis of a 2-amino-2-deoxypentose which is probably the L-ribose derivative in view of the work of Lemieux and Chu [*ibid.*, **80**, 4745 (1958)].

(10) (a) W. H. Myers and G. J. Robertson, *ibid.*, **65**, 8 (1943); (b) B. R. Baker and R. E. Schaub, *J. Org. Chem.*, **19**, 646 (1954).

(11) D. L. MacDonald and H. O. L. Fischer, THIS JOURNAL, **74**, 2087 (1952); *Biochim. et Biophys. Acta*, **12**, 203 (1953).